REMARKS

With this Amendment, Claim 1 has been deleted. New Claims 2-21 have been added. Claim 2 is supported by the specification on page 7, lines 13-page 8 line 15. Claim 3 is supported on page 14, line 20-page 15, line 10 of the specification. Claims 4-5 are supported on page 9, lines 14-19 of the specification. Claim 6 is supported on page 7, lines 20-22 of the specification. Claim 7 is supported on page 10, lines 7-12 and page 7, lines 13-19 of the specification. Claim 8 is supported on page 28, line 20-page 29 line 1 of the specification. Claim 9 is supported on page 10, lines 13-15, page 30, lines 1-2, page 31, lines 17-19 of the specification. Claim 10 is supported on page 28, lines 21-page 29, line 1 of the specification.. Claims 11-15 are supported on page 10, lines 4-13; page 11, lines 15-16 and page 28, lines 10-14 of the specification. Claim 16 is supported on page 14, lines 8-19 of the specification. Claim 17 is supported on page 17, lines 8-9 of the specification. Claim 18-20 are supported on page 15, line 21- page 16, line 5 of the specification. Claim 21 is supported on page 18, lines 18-23 of the specification. Claim 22 is supported on page 13, lines 9-17 of the specification.

Amendments to the specification are made to correct a number of minor typographical and grammatical errors. In addition, being filed herewith is a Request for Approval of Amendments to the Drawings with substitute drawings for Figures 2 and 3 which have been revised to have a light background to facilitate reproduction. No new matter is introduced by any of these amendments.

CONCLUSION

In light of the amendments, Applicants are of the opinion that the application is now in condition for allowance. Such action is respectfully requested. If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,

KILPATRICK STOCKTON LLP.

Dated: 10-28-02

By: Eleanor M. Musick
Reg. No. 35,623

KILPATRICK STOCKTON, LLP
1100 Peachtree St.
Suite 2800
Atlanta, GA 30309-4530
Phone: (404) 815-6500
Attorney Docket: 4008US (43413-261017)

Marked copy of the amendments

Please replace the paragraph on page 6, lines 4-9 with the following:

This system and method employs the use of gene expression microarrays. For example, microarrays consisting of full length genes or gene fragments on a substrate may be formed. These arrays can then be tested with samples treated with [a] substances to elucidate the gene expression pattern associated with treatment with the substance. This gene pattern can be compared with gene expression patterns of compounds associated with known toxicological responses.

Please replace the paragraph on page 8, lines 10-15 with the following:

In a further preferred aspect of this embodiment, the summary scores are subjected to logistic regression analysis, resulting in a predictive model. In this aspect of the embodiment, the input data are the summary scores per sample, which is an indicator for each sample; the analysis is a logistic regression analysis mapping the summary scores to a 0 to 1 scale of toxicity; and the out[ ]put data are one or [ort] more mathematical formulae that [converts] convert a column of average differences into a single 0 to 1 toxicological score for a sample.

Please replace the paragraph on page 9, lines 1-3 with the following:

In correlating these other studies, one preferably [compare] compares gene lists for patterns of interest between studies of related compounds to arrive at a consensus set of genes involved in a toxicological response.

Please replace the paragraph on page 9, lines 4-10 with the following:

In another preferred embodiment of the present invention, the goal of the method for assessing the toxicity and toxicology of a substance is to use gene expression to predict whether a compound has a high probability of being toxic at a given dose. In this preferred embodiment, patterns of gene expression can be compared against [know] known "toxic" patterns and a similarity score calculated. Preferably, the methodology associated with this preferred embodiment includes identification of gene expression patterns associated with toxicity; quantification of this association; development of a statistical inference of similarity; and validation of results.

Please replace the paragraph on page 9, lines 11-13 with the following:

It will be appreciated that in such a modeling, there [cam] can be a number of different types of markers, including general markers, group markers (for example, cholestasis, necrosis, stenosis), and compound specific markers.

Please replace the paragraph on page 9, lines 20-24 with the following:

In another preferred embodiment of the present invention, there are various stages of model development. These[,] preferably[,] include: selection (determination of relevant expression patterns that are time stable and dose dependent); quantification (production of composite measures that define patterns); prediction (use of composite measures to assign probability of

Please replace the paragraph on page 22, lines 18-23 with the following:

The term "mismatch control" refers to a probe that has a sequence deliberately selected not to be perfectly complementary to a particular target sequence. The mismatch control typically has a corresponding test probe that is perfectly complementary to the same particular target sequence. The mismatch may comprise one or more bases. While the mismatch(s) may be [locates] located anywhere in the mismatch probe, terminal mismatches are less desirable as a terminal mismatch is less likely to prevent hybridization of the target sequence. In a particularly

Please replace the paragraph on page 27, lines 4-9 with the following:

For example if a single [does] doses of a drug and a vehicle is administered at three time points. Then, for each time point a gene would demonstrate a basic pattern of either upregulated, downregulated, or not significantly changing. The number of patterns produced would then be three for each time which would mean that 3 x 3 x 3- = 27 patterns can be produced. When [we have] one has multiple doses and a larger number of time points, the number of patterns can be extensive. But only a small number of these patterns are useful.

Please replace the paragraph on page 28, lines 3-6 with the following:

With regard to quantification of the toxicological response, principal component analysis (PCA) is employed. [Here for] As an input, genes are selected for patterns that are biologically relevant to the toxicological process. Then, PCA analysis is performed on all samples. The resultant output is 1 to 8 summary scores for each sample.

Please replace the paragraph on page 29, lines 1-11 with the following:

multidimensional scaling, clustering, and neural networks. A general discussion of each technique can be found in "Multivariate Analysis, Prentice Hall ISBN 0-13-894858," which is incorporated herein by reference. All of these methods work by making composite measures from the many measurements taken from each object. With gene expression patterns there are [we have] several time and dose points which represent multiple objects that are grouped together. None of these techniques are sufficient alone to represent this order of complexity. Contrast analysis allows [us] one to identify measurements that are partial independent of time beeause they are time stable yet are affected by toxic doses more then non toxic doses. The PCA combines these many measurements into a series of orthogonal composite measures. Since these composite measures are non correlated by definition the problem of multicolinearity which can decrease the power of logistic regression is eliminated. By combining these techniques in the order described many of the limitations of each individual technique is reduced.

Please replace the paragraph on page 31, lines 1-4 with the following:

This model is used to predict the probability of toxicity for each of the J samples. If the probability for the known toxins is consistently high and the probability for the known non-toxins is consistently low, then the model is accepted. Otherwise, [alter] the gene selection criteria is altered, and [redo] the multivariate statistical analysis is repeated.

Please replace the paragraph on page 31, lines 5-14 with the following:

The invention consists of three distinct stages. At each stage, small variations in technique can be used to accomplish the same task. The first stage, selection of time stable and dose dependent patterns by contrast analysis, can be altered by changing the method of measuring variation. [We use a] The method used [that] is

based on analysis of variance, where the time component and dose component are assessed simultaneously. One could use a series of t test on individual parts of the pattern to get a collective set of p values that could approximate our method of measuring variation. One could also set an arbitrary fractional cutoff, mean or median of experimental group divided by control group, to approximate the measurement of variation for each part of the pattern that is then use in the next to stages of analysis. The novel feature is to find time, stable and dose dependent patterns with a predicted p value for that pattern.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arthur L. Castle *et al.*

Serial No.: **10/052,547** — Examiner:

Filed: **January 23, 2002** — Art Unit: **1645**

For: **Method and System for Predicting the Biological Activity, including Toxicology and Toxicity, of Substances**

REQUEST FOR APPROVAL OF AMENDMENTS TO THE DRAWINGS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully request approval of the amended drawings filed herewith.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents and Trademarks, Washington, DC 20231, on **October 28, 2002**.

Eleanor M. Musick - Reg. No. 35,623

MEHB 2-27-72

REMARKS

Upon review of the drawings as originally filed, it was determined that the dark background in Figures 2 and 3 had made copying of the figures difficult and that the figures were not as clear as they could be. In the amended figures filed herewith, the dark background has been eliminated and the points on the plot have been made to include numerical indicators corresponding to the class (Classes 1 through 7) to which the points belong. The legend previously provided at the right side of the plots has been eliminated and the class designations are moved to locations near the points belonging to the respective classes. No new matter is added by these amendments.

It is respectfully requested that the amendments described herein be approved. A full set of formal drawings will be submitted upon receipt of a notice of allowance.

Should the Examiner have any questions or comments, he is invited to contact the undersigned attorney for Applicants.

Respectfully submitted,

KILPATRICK STOCKTON LLP.

Dated: 10-28-02

By: Eleanor M. Musick
Reg. No. 35,623

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